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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/823,006	04/12/2004	Andrea G. Cochran	11669.118USD1	5028

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EXAMINER	
WESSENDORF, TERESA D	

ART UNIT	PAPER NUMBER
1639	

DATE MAILED: 06/29/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/823,006	COCHRAN ET AL.	
	Examiner	Art Unit	
	T. D. Wessendorf	1639	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 April 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *19-27* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *19-27* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of Claims

Claims 19-27 are pending in the application and under examination.

Withdrawn Objection and Rejection

In view of the amendments to the specification the objection has been withdrawn. Also, in view of the amendments to the claims and applicants' arguments the rejections under 35 USC 112, first (written description) and second paragraph has been withdrawn.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 19, as amended, is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the

inventor(s), at the time the application was filed, had possession of the claimed invention. {This is a new matter rejection].

The claimed "scaffold comprising first and second opposite strands" is not supported in the as-filed specification. Applicants point the support at e.g., page 10, line 24. A review of the cited sections does not provide support for the newly added limitation.

Claim Rejections - 35 USC § 112, second paragraph

Claims 19-27, as amended, are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention for reasons of record.

Claim 19 is confusing as to the library of peptide being prepared. It is not clear how a single step method forms the plurality of peptides having the recited properties. The claim describes more a compound rather than a method of preparing said compound library. Does the scaffold comprise a first and second opposite strands or each strand is the presented turn sequence? It is not clear as to the amino acid comprised in the presented turn sequence. Is this different from the WX1W turn? It is not

clear as to which presented turn sequence comprises random amino acids. Is a library different from the recited plurality of peptides?

Claim Rejections - 35 USC § 103

Claims 19-27, as amended, are rejected under 35 U.S.C. 103(a) as being unpatentable over Cochran et al (WO 0077194) for reasons of record and reiterated below.

Cochran discloses at page 15, line 13 up to page 23, line 6 a method of synthesizing a library of peptide containing a W-W cross strand. Cochran states that many methods for generating peptide libraries that are known in the art can be used to generate the libraries of the instant invention. Cochran further discloses at page 9, line 23 up to page 10, line 27 that disulfide cyclization is helpful, although not sufficient to constrain the structure of many peptides. The rest of the residues of the peptide are further selected to be significantly biased toward the formation of the hairpin structure. A subset of the residues within the peptide of the invention is varied to provide relative diversity for mimicking various bioactive peptides having a identified secondary structure, such as beta turn. Cochran further states at page 10, lines 22-29 that "… variations can occur at non-hydrogen bonded strand sites (e.g.,

A1/A5)….. and its cross -strand counterpart(e.g., A1/A5 or A2/A4) can have same or different amino acids…." See also page 14, lines 6-10 wherein Cochran made an analogy to the WW domains. Cochran discloses or at least suggests that D-cys at one or both ends was not compatible with the cross-strand geometry of hairpins (as initially thought of said disulfide bond geometry). Since Cochran discloses or at least suggests the WW domains hence, it would be within the ordinary skill in the art to pick and choose the specific residues taught in the generic formula. The suggested teachings of Cochran that cys has not been used before would have led one to remove the cys residues especially since Cochran discloses that the cross strand occurs between the W-W residues. Note that Cochran discloses or directs primarily the experiments to the peptide sequence responsible for the turn sequence (without the presence of Cys).

Response to Arguments

Applicants argue that the Cochran reference recite the peptides of the invention are cyclized via disulfide bonds between two cys within the peptide sequences. The claimed invention recites the trp residues from a cross-strand pair without any disulfide bond. Cochran does not disclose or suggest

any advantage to structurally constrained peptides that do not have a disulfide bond as recited by the claims.

In response, Cochran does not have to disclose the advantage to structurally constrained peptides to make a peptide with or without a disulfide bond. The claims are drawn to method of making the compound library, not to a compound library. The claims do not recite for a specific step that preclude cys-cys in the compound library especially in the absence of what is included or precluded by the claimed structurally constrained peptides. Rather, as acknowledged by applicants in the instant REMARKS (4/21/2006, page 7) referring to page 11, line 20 to page 12, line 19 of the instant specification, the method of making a library of peptide is known. The method of making must be known since the compound being synthesized i.e., the wild type-Thr containing is a known compound. Whether the peptide contains a disulfide bond or not the same process steps of e.g., chemical synthesis is used to make the peptide. Hence, the single claim step. [Chemical synthesis is a markedly advanced method, that it is now automated, whether the peptide contains two cys or not]. Note that Cochran discloses or directs primarily the experiments to the peptide sequence responsible for the turn sequence (without the presence of Cys).

Applicants argue that under obviousness analysis, the examiner must consider the prior art reference as a whole. Cochran is argued to teach the advantage of scaffolds having disulfide bonds. One would not be motivated to remove disulfide residues form the peptide. Applicants argue that it was surprising that a peptide scaffold having at least two Trp-Trp cross-strand pairs was soluble, given that in some embodiments one of the residues are Trp.

In reply, again much of applicants' arguments are drawn to the claimed compound rather than to the differentiating step of the claimed single step to the step taught by Cochran. Cochran discloses that the method of preparing (synthesizing) a peptide containing a disulfide(i.e., Cys-Cys) or without a disulfide is well known in the art. In considering disclosure of a reference, it is proper to take into account not only specific teachings of the reference but also "inferences" which one skilled in the art would reasonably be expected to draw therefrom. In re Preda, 159 USPQ 342; In re DeLise 160 USPQ 806.

Claims 19-27, as amended, are rejected under 35 U.S.C. 103(a) as being unpatentable over Robinson et al (US 6,878,804) in view of Floudas et al (US 2003/0036093) for reasons of record, as repeated below.

Robinson et al discloses at col. 5, line 47 up to col. 7, line10 a method of constructing a library of structurally-constrained peptides comprising the synthesis of template-fixed cyclic peptides of general formula I which mimic the various naturally occurring beta-hairpin conformations (see e.g. the Figures, Example 1). Template structures corresponding to above formulae (a) through (h) have been shown to stabilize the H-bond network present in beta-hairpins. The beta-hairpin motif consists of two antiparallel beta-strands linked by a short loop or turn and have been classified depending on the H-bonding network. Robinson discloses that in large surface protein interfaces, there are hot spots of binding energy made up of a small subset of residues in the dimer interface. These hot spots are enriched in tryptophan (Trp), tyrosine (Tyr) and arginine (Arg), and are surrounded by energetically less important residues. The beta-hairpin loop motif offering two opposite beta-sheet surfaces (e.g. a hydrophobic and a hydrophilic face) for possible binding interactions is ideally suited to meet the criteria for surface interactions. See specifically, Example 6, at col. 38 and also, examples 25-40 at col. 41, which discloses a cyclic peptide occurring at the R and K residues. Robinson similarly taught or at least suggests that the dimer interface can also be trp. Robinson does not disclose a zipper-like motif

of the trp residues. However, Floudas discloses at paragraph [0152] that the beta sheet nucleates at the hairpin turn and proceeds to form through a zippering model that is stabilized by hydrogen bond formation. Floudas at [0153] discloses that hydrophobic interactions between beta strand residues are used to develop several optimization models that can be globally optimized to provide a rank ordered list of potential beta sheet arrangements with decreasing hydrophobic interaction energies. These formulations are classified as inter alia, a strand-based model. At paragraph [0154] it is disclosed that the strand-based formulation relies on the identification of contiguous sets of residues to define potential beta strands. These individual strands represent one component in the formation of a beta sheet configuration. Accordingly, it would have been obvious to one having ordinary skill in the art at the time the invention was made to choose Trp-Trp as the cross-strand zipper-like motif in the method of Robinson since Robinson teaches that Trp is one of the cross-strand forming residues. As taught by Floudas this forms a zipper-like motif that are used to develop several optimization models that can be globally optimized to provide a rank ordered list of potential beta sheet arrangements with decreasing hydrophobic interaction energies. This teaching of

Floudas would provide the motivation to one having ordinary skill in the art at the time of the invention.

Response to Arguments

Applicants argue that Robinson discloses beta-hairpin loop mimetics that are fixed to a template, as shown in Formula I, col. 1. The template fixation constrained peptides into a cyclic formation. Robinson provides no motivation to generate structurally constrained peptides using the Trp-Trp cross-strands recited by the claims in place of he template fixation techniques.

In response, attention is drawn to the suggested teachings of Robinson at e.g., col. 5, line 47 up to col. 7, line 10. Robinson discloses that in large surface protein interfaces, there are hot spots of binding energy made up of a small subset of residues in the dimer interface. These hot spots are enriched in tryptophan (Trp), tyrosine (Tyr) and arginine (Arg), and are surrounded by energetically less important residues. Example 6, at col. 38 and also, examples 25-40 at col. 41, discloses a cyclic peptide occurring at one of the hot spots i.e., R and K residues. Robinson similarly taught or at least suggests that the dimer interface can also be trp. In considering disclosure of a reference, it is proper to take into account not only specific teachings of the reference but also "inferences" which

one skilled in the art would reasonably be expected to draw therefrom. In re Preda, 159 USPQ 342; In re DeLise 160 USPQ 806.

Applicants' arguments with respect to Floudas are noted. Also, the arguments as to the stability and solubility of the peptide scaffold of the at least two Trp-Trp cross-strand is noted. However, even without Floudas (per the amended claims), the Robinson's method of making the peptide library suffices. The stability property of the peptide scaffold comprising at least two Trp-Trp strand pairs do not add any limitation to a method as claimed comprising only the known single step of chemical synthesis.

No claim is allowed.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to T. D. Wessendorf whose telephone number is (571) 272-0812. The examiner can normally be reached on Flexitime.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras can be reached on (571) 272-4517. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

T. D. Wessendorf
Primary Examiner
Art Unit 1639

Tdw
June 23, 2006